IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: **Lichtenberger, Lenard M.**	§
	§ EXAMINER: **JIANG, SA**
SERIAL NO: **09/827,493**	§
	§ GROUP ART UNIT: **1617**
FILED: **04/06/01**	§
	§ DOCKET: **96606/15UTL**
FOR: **UNIQUE COMPOSITION OF ZWITTERIONIC PHOSPHOLIPIDS AND BISPHOSPHONATES WITH REDUCED TOXICITY AND ENHANCED BIOAVAILABILITY**	§

EV 510 916 515 US Number	**CERTIFICATE OF MAIL BY EXPRESS MAIL**	September 28, 2004 Date of Deposi
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Robert W. [illegible]		September 28, 2004 Date of Signature

BRIEF ON APPEAL

(1) *Real Party in Interest*

The real party in interest is the Board of Regents of the University of Texas System, the assignee of the entire interest in the above application.

(2) *Related Appeals and Interferences*

There are no other appeals or interferences known to appellant, the appellant's legal representative or the assignee which will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

(3) *Status of Claims*

This appeal is from the final rejection of all pending claims dated 23 February 2004 and an Advisory Action maintaining the Final Rejection dated 11 August 2004.

(4) *Status of Amendments*

All claims stand rejected under 35 U.S.C. § 103(a) are unpatentable over DAIFOTIS,

et al. (WO 9904773, of record) in view of Lichtenberger et al. (5,763,422, of record), further in view of Hovancik et al. (5,869,471, of record), where the Examiner contends:

The Examiner contends as follows:

Daifotis et al. discloses that bisphosphonates such as atendronate, risedronate, tiludronate and ibandronate, within the instant claims, are known to be useful in pharmaceutical compositions and methods for treating osteoporosis. See abstract, page c 1 lines 14-15 and page 2 lines 1-15. Daifotis et al. also discloses that bisphosphonates are known to have low bioavailability from GI tract and therefore cause adverse GI effects. See abstract, page 1-3. Further, Daifotis et al. discloses that the purpose of the methods therein are for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the adverse GI effects (see abstract and page 7 lines 22-23 in particular). Daifotis et al. also discloses the effective amounts of bisphosphonates to be administered in the compositions therein for minimizing the adverse GI effects (see Examples at page 24-27).

Daifotis et al. do not expressly disclose the employment of one zwitterionic phospholipid to reduce GI toxicity of brsphosphonate when administering at least one bisphosphonate in a pharmaceutical composition. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.

Lichtenberger et al. disclose that zwitterionic phospholipids, within the instant claims, (see abstract, col. 3 lines 59-67, col. 10 lines 50-62, col.11 .lines 60-65) are capable of reducing GI irritating (adverse) effects and is therefore useful broadly in combining with many NSAID drugs (see Table I at col.4 lines 25-52) in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, *e.g.*, inducing GI ulcers and bleeding. See also abstract and col.1-2. Lichtenberger et al. also disclose the effective amounts of zwitterionic phospholipids in the pharmaceutical compositions therein. See col.12 lines 12-34.

Hovancik et al. discloses that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treatfng arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine one zwitterionic phospholipid to reduce G1 toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition since zwitterionic phospholipids are known to be capable of reducing GI irritating (adverse)

effects that caused by other drugs such as many NSAIDs according to Lichtenberger et al. Moreover, bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate are known to cause adverse GI effects and the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonates. Further, the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders.

Therefore, one of ordinary skill in the art would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate. Hence, the combined teachings of Daifotis and Lichtenberger Hovancik have provided the motivation of the instant invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts or ratio of zwitterionic phospholipid and a bisphosphonate in a composition because the effective amounts of zwitterionic phospholipid to the administered are known in the art. Moreover, the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch,* 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks and the declaration of Dr. Lenard M. Lichtenberger (inventor) submitted October 7, 2003 under37CFR 1.132 with respect to this rejection of claims 1-32 made under 35 U.S.C. 103(a), of record stated in the Office Action dated May 7, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for as further discussed below.

Again, Applicant arguments that there is no motivation to combine because there is no reasonable expectation that their combination would be successful are not found persuasive. As Applicant admits, Daifotis et al. clearly teaches that bisphosphonates can cause adverse GI effects when ingested. Daifotis et al. also disclose that their invention relates to methods for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the occurrence of or potential for adverse GI effects (see page 1 lines 11-13). Thus, the teachings of Daifotis et al. are seen to provide the motivation to make the present induced by bisphosphonates.

Moreover, zwitterionic phospholipids (within the instant claims) are known to be capable of reducing GI irritating (adverse effects) and are

therefore useful broadly in combining with NSAID drugs in pharmaceutical compositions in order to reduce GI adverse effects, e.g., inducing GI ulcers and bleeding, caused by NSAID drugs, according to Lichtenberger et al. As discussed in the previous Office Action, one of ordinary skill in the art, therefore, would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonatein a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate with a reasonable expectation for success, absent evidence to the contrary.

Additionally, Hovancik et at. has been cited by the examiner primarily for its teachings of that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7), further supports the examiner's position, since that the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders. Thus, one of ordinary skill in the art would reasonably expect that the combination of bisphosphonates and zwitterionic phospholipids would be successful in treating bone disorders, the same disorders, absent evidence to the contrary.

Applicant's arguments regarding that "the motivation to combine these to references is derived exclusively from hindsight" have been considered but are not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Therefore, as discussed above, motivation to combine the teachings of the prior art to make the present invention is seen and no improper hindsight is seen. The claimed invention is clearly obvious in view of the prior art.

Dr. Lichtenberger's second declaration herein is ineffective to overcome the 103(a) rejection herein since it is not seen to provide clear and convincing evidence of nonobviousness or unexpected results. The declaration merely presents the testing result for the single particular bisphosphonate, risedronate, in combination wth the single particular zwitterionic phospholipid, DPPC, and/or also combining indomethacin (a NSAID), to be administered orally to rats. However, the evidence in the declaration is not commensurate in scope with the claimed invnetion and does not demonstrate criticality of a claimed range of the bisphosphonate (a genus) and zwitterionic phospholipids (a genus) in the claimed composition.

Further, Applicant asserts that "This data shows just how unpredictable combinations of even well known pharmaceuticals can be." Nonetheless, the

data in diagrams, figures, and tables herein are unclear as to how the graphical, diagram and table presentations herein may be taken to demonstrate unexpected effect in the instant invention. Moreover, the clear explanation of pointing out exactly what facts are established therein are relied upon by applicant is not seen in the declaration. Applicant has the burden to explain the experimental evidence. See In re Borkowski and Van Venrooy 184 USPQ 29 (CCPA 1974).

Therefore, the declaration is insufficient to rebut the prima facie case herein.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefor, said rejection is adhered to.

23 February 2004 Final Office Action.

(5) *Summary of Invention*

The present invention relates to pharmaceutical compositions and oral medications including a bisphosphonate and a zwitterionic phospholipid. The inclusion of phospholipids have reduced the gastric toxicity of the bisphosphonates and increased their bioavailibility. It is the ability for zwitterionic phospholipids to protect the GI tract and increase the bioavailibility of these drugs that is unexpected over the prior.

(6) *Issues*

(A) Whether the inventions encompassed by claims 1-32 and 46-48 are unpatentable over DAIFOTIS, et al. (WO 9904773, of record) in view of Lichtenberger et al. (5,763,422, of record), further in view of Hovancik et al. (5,869,471, of record).

(7) *Grouping of Claims*

Claims 1-21, 22-24, 25-29 and 46-47 relate to pharmaceutical compositions for treating osteoporosis including a bisphosphonate and a zwitterionic phospholipid.

Claims 30-32 and 48 relate to oral medication for treating osteoporosis including a bisphosphonate and a zwitterionic phospholipid.

(8) *Argument*

(A) Applicant asserts that this invention is non-obvious over the cited prior art because the present invention is a compositional solution to the problem of GI toxicity of bisphosphonates; a problem that has plagued the treatment of osteoporosis with bisphosphonates, since their FDA approval starting in the 1990's, while significantly improving the bio-availability of the bisphosphonates. Moreover, the primary reference disclosed a solution to the bisphosphonate GI toxicity problem, yet the Examiner relies on this reference as the basis for an obviousness rejection. How can a reference that solved a problem now be relied on as reference suggesting a completely different solution?

1. The Examiner relies as the primary reference Daifotis, et al. to build the obvious rejection. However, Daifotis et al. **solved** the GI toxicity problem by developing an administration protocol that substantially reduces or eliminates GI toxicity of bisphosphonates. Thus, in the first instant, Applicant contends that reliance on Daifotis et al. is misplaced as a primary reference. An ordinary artisan would read Daifotis et al. and assume that there is no reason to do any more work on the GI toxicity of bisphosphonates because Daifotis et al. solved the problem in a simply straight forward manner. Applicant, therefore, strongly urges that an ordinary artisan would look to Daifotis et al. as suggesting an alternate means to solve bisphosphonate GI toxicity – Daifotis et al. had already solved the problem.

2. The deficiencies of Daifotis et al. are not just limited to the "We Solved the Problem" factor, but also include the fact that Daifotis et al. includes no disclosure, teaching or suggestion that would direct one of ordinary art to combine the Daifotis et al. administration protocol with an agent that may be effective in reducing GI toxicity *ab initio*. The problem with administrative protocol solutions to an adverse drug problem is that it requires cooperation from the patient to successfully implement the solution. This administrative fix is further complicated by the significantly adverse synergistic enhancement of bisphosphonate GI toxicity when an NSAID is taken during bisphosphonate administration as set forth in Hovancik et al. and in Dr. Lichtenberger's Second Declaration. Nowhere in Daifotis et al. is there a suggestion that a compositional solution to bisphosphonate GI toxicity is possible. In fact, a fair reading of Daifotis et al., would clearly suggest to an

ordinary artisan that there is simply no need for any other solution to the problem – a simply administration protocol can eliminate all GI toxic effects of bisphosphonates.

2. Because Daifotis et al. make absolutely no suggestion of an alternate solution to the problem of bisphosphonate GI toxicity, Daifotis et al. cannot be relied on as suggestive of a compositional fix to the GI toxicity of bisphosphonates. Daifotis et al. only speaks to the GI toxicity problem of bisphosphonates in the context to disclosing the solution to the problem, not in a context of suggesting an alternate approach. Without some suggestion in the art to combine, the combination is cannot supportable.

3. The present invention, instead of being an administration protocol solution to the GI toxicity problem of bisphosphonates, is a compositional solution. The need for a compositional solution to the problem is further exacerbated by the frequent co-administration of both a bisphosphonate to treat osteoporosis and an NSAID to ameliorate inflammation and pain associated with bone disorders or to reduce the risk of cardiovascular disease. The combination of bisphosphonates and NSAIDs has resulted in a significantly increased risk of GI ulceration even when the NSAID is given intravenously and the bisphosphonate is given orally. See Second Dr. Lichtenberger Declaration. Thus, the basic GI toxicity of bisphosphonates and of NSAIDs are significantly and synergistically increased when the drugs are taken in combination. See Second Dr. Lichtenberger Declaration. Thus, Hovancik et al. instead to supporting the obviousness of the present invention demonstrates just how such drug interactions are unpredictable.

4. The present invention is a compositional fix to the problem. Not only does the compositional remedy the basic toxicity of bisphosphonates, it is also effective in more than halving the synergistic increase in GI toxicity of co-administered bisphosphonates and NSAIDs, a synergistic effect that is seen even when the bisphosphonate is given orally and the NSAID is given intravenously. See Figure 4 of this application and the Second Dr. Lichtenberger Declaration. Thus, this compositional solution to the GI toxicity problem answers a long felt need in the general administration of bisphosphonate, but also answers the new problem of co-administration of NSAIDs and bisphosphonates.

5. Applicant also rejects that contention that it is obviousness that phospholipids would

reduce the GI toxicity of bisphosphonate. While it is true that phospholipids have been shown to be effective agents, when pre-associated with NSAIDs, in reducing the GI toxicity of the NSAIDs, such an observation does not support the general proposition, that phospholipids will work to lower GI toxicity and increase bio-availability for all drugs, especially drugs that are radically different structurally from NSAIDs.

6. Dr. Lichtenberger has submitted data demonstrating the fact that bisphosphonates are highly competitive with phospholipids for sites of a model hydrophobic membrane. First Declaration Dr. Lichtenberger. Based on this data, an ordinary artisan could well conclude that the inclusion of a phospholipid would greatly increase the GI toxicity of a bisphosphonate by increasing the amount of bisphosphonate at or near the GI mucosal lining. Thus, an ordinary artisan could have well reasoned that a bisphosphonate-phospholipid combination may have resulted in increased GI toxicity by increasing the relative concentration of the bisphosphonates at the stomach lining. The fact, that the opposite occurred was only clear after the experiment was performed. Applicant is not suggesting that an ordinary artisan could not have suggested that bisphosphonate-phospholipid combination would reduce GI toxicity, but in the absence of actual data, either eventually would be mere speculation with each being possible *ab initio*. Just like any civil court proceeding, prior to a judgment either party can win, only after the judgment is handed down does the winner become obvious. Thus, **only** in hindsight can one now claim that the latter theory was correct and the former theory incorrect, such is the world of science.

7. The addition of Hovancik et al. further confusions the situation and makes the Examiner's obviousness argument less strong, and renders the obviousness argument even less tenable, because the unexpected consequence of co-administering an NSAID and a bisphophonate results in a significant and synergistic increase in the very problem that the present invention is designed to solve. As shown in data set forth in a Second Dr. Lichtenberger Declaration, oral administered bisphosphonate and intravenous administered NSAID demonstrates a dangerous synergistic increase in GI toxicity of bisphosphonates. The data in the attached figures show that a particular bisphosphonate had little toxicity and a particular NSAID had moderate toxicity, but when co-administered by different

administration pathways, the resulting GI toxicity was 10 or more times higher for the bisphosphonate and several time higher for the NSAID.

8. Applicant, therefore, believes that even if it were proper to combine of Daifotis et al. and any Lichtenberger NSAID references, the combination does not render the present invention obvious because nothing in Daifotis et al. suggest combining the their teaching, a administration solution, with Lichtenberger's compositional solutions to NSAID toxicity. There simply nothing in the cited references to suggest such a combination. Again Daifotis et al. can be fairly read as teaching squarely away from such a combination, they solved the problem, and Lichtenberger makes no reference to bisphosphonates or to other pharmaceutical having structures radically different from NSAIDs.. Daifotis et al. states and claims a cure to the basic problem the Examiner now believes Daifotis et al. suggest should be cured by adding a phospholipid, but this contention flies fully in the face of the Daifotis et al. teaching – ordinary artisan look no farther for we have eliminated this problem. Such a statement teaches squarely away from the present invention – the problem is solved.

10. The combination of Daifotis et al., Lichtenberger and Hovancik et al. do not render the present invention obvious because none of these reference suggests combining bisphosphonates with phospholipids. Daifotis et al. solved the very problem the present application solved in a different way. Daifotis et al. suggests that there is no reason to look for an alternate solution as they solved the problem. L ichtenberger, while solving the problem of NSAID GI toxicity, did not suggest that phospholipids would solve GI toxicity problem of drugs having substantially different structures than NSAIDs. And Hovancik et al., coupled with the data in Dr. Lichtenberger's Second Declaration, shows how unpredictable the side effects of drug combinations are. Thus, the combination of the three references only in hindsight lead to the present invention.

9. In summary, the primary reference does not disclose, teach or suggest looking for any alternate solution to the problem of bisphosphonate GI toxicity – the primary reference, Daifotis et al. solved the problem by an administration protocol. The Lichtenberger references clearly teach the phospholipids reduce GI toxicity of NSAIDs, but does not suggest their application to pharmaceuticals having radically different chemical compositions

as compared to NSAIDs. And Hovancik et al. simply stands for the proposition that the effects of drug combinations are difficult to determine and often lead to adverse side affects.

If additional information or communications are needed during the pendency of this Appeal, the Patent Office can contact Applicant's attorney at 713.977.7000 or by email at rwstroz@flash.net.

Respectfully submitted,

Date: **September 28, 2004**

Robert W. Strozier
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(9) *Appendix - Copy of Claims involved in this Appeal*

This appeal is from the final rejection of claims 1-32 and 46-48. Claims 33-45 were withdrawn and relate to a non-elected group and are not at issue here. Claims 1-32 and 46-48 read as follows:

1.(**original**) A pharmaceutical composition for treating osteoporosis comprising at least one zwitterionic phospholipid and at least one bisphosphonate.

2.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid is present in an amount sufficient to reduce GI toxicity of the bisphosphonate and the bisphosphonate is present in an amount sufficient to reduce bone resorption.

3.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid is present in an amount sufficient to reduce GI toxicity of the bisphosphonate and improve bisphosphonate bio-availability when the composition is taken with food and the bisphosphonate is present in an amount sufficient to reduce bone resorption, increase in bone density and/or reduce bone fractures.

4.(**original**) The composition of claim 3, wherein the amount of bisphosphonate is between about 0.1 mg per dose and about 1000 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.1 and about 1:100.

5.(**original**) The composition of claim 3, wherein the amount of bisphosphonate is between about 1 mg per dose and about 500 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.5 and about 1:50.

6.(**original**) The composition of claim 3, wherein the amount of bisphosphonate is between about 2 mg per dose and about 50 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:1 and about 1:10.

7.(**original**) The composition of claim 3, wherein the amount of bisphosphonate is between about 2 mg per dose and about 20 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:1 and about 1:5.

8.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid is present in an amount sufficient to reduce GI toxicity of the bisphosphonate and the bisphosphonate is present in an amount sufficient to reduce bone resorption, increase in bone density and/or reduce bone fractures.

9.(**original**) The composition of claim 8, wherein the bisphosphonate is present in an amount between about 0.1 mg per dose and about 1000 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.1 and about 1:100.

10.(**original**) The composition of claim 8, wherein the bisphosphonate is present in an amount between about 1 mg per dose and about 500 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.5 and about 1:50.

11.(**original**) The composition of claim 8, wherein the bisphosphonate is present in an amount between about 2 mg per dose and about 50 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:1 and about 1:10.

12.(**original**) The composition of claim 8, wherein the bisphosphonate is present in an amount between about 2 mg per dose and about 20 mg per dose and a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:1 and about 1:5.

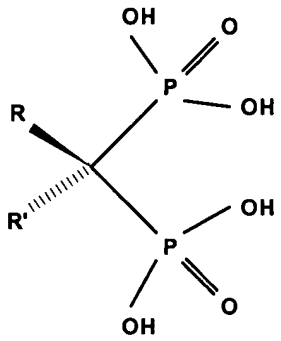
13.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid increases the bio-availability of the bisphosphonate from about 2 to about 20 fold.

14.(**original**) The composition of claim 1, wherein the bisphosphonate is in its zwitterionic form and forms an ionic association complex with the zwitterionic phospholipid.

15.(**original**) The composition of claim 1, further comprising a colloidal metal, a metal complex or a mixture or combination thereof.

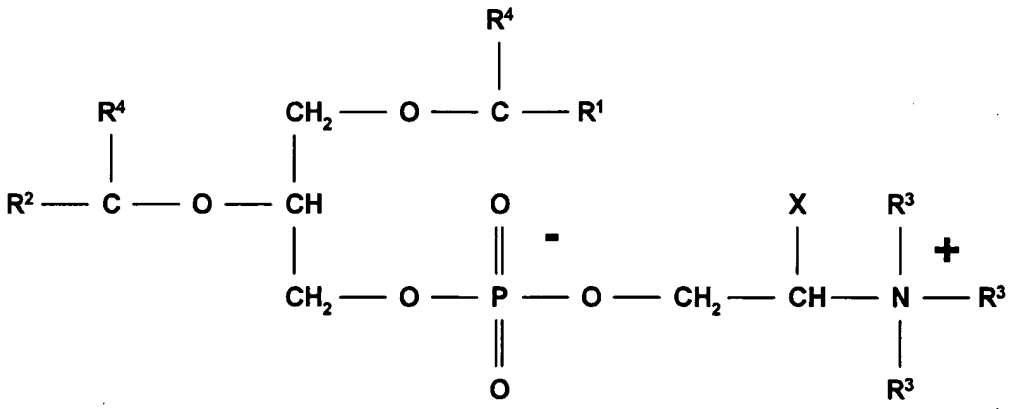
16.(**original**) The composition of claim 1, wherein the bisphosphonate is characterized by the general formula (I):

(I)



where R' is H, OH or Cl and R is: (a) an alkyl group having 1 to 6 carbon atoms, optionally substituted with amino, alkylamino. dialkylamino or heterocyclyl, where the alkyl groups in alkylamino and dialkylamino substituents have 1 to 5 carbon atoms and are the same or different in the case of the dialkylamino substituted alkyl groups; (b) a halogen; (c) an arylthio, preferably chlorosubstituted; (d) a cycloalkylamino having 5 to 7 carbon atoms; or (e) a saturated five or six membered nitrogen containing heterocyclyl having 1 or 2 heteroatoms.

17.(**original**) The composition of claim 1, wherein the phospholipid is characterized by the of general formula (II):

(II) 

where R_1 and R_2 are saturated or unsaturated substitutions ranging from 8 to 32 carbon atoms; R_3 is H or CH_3, and X is H or COOH; and R_4 is =O or H_2.

18.(**original**) The composition of claim 1, wherein the bisphosphonate is selected from the group consisting of 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate), N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (mildronate, olpadronate), I-hydroxy-3- (N-methyl-N-pentylamino) propylidene-1,(N-methyl-N-pentylamino) propylidene-1, 1-bisphosphonic acid (ibandronate), I-hydroxy-2-(3-pyridyl) ethylidene-1,(3-pyridyl) ethylidene-1, 1-bisphosphonic acid (risedronate), 1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate), 1-hydroxy-3- (l-pyrrolidinyl) propylidene-1,1-bisphosphonic acid, l-hydroxy-2- (1-imidazolyl) etylidene-l, 1-bisphosphonic(1-imidazolyl) etylidene-l, 1-bisphosphonic acid (zoledronate), 1-hydroxy-2- (imidazo [1,2-a] pyridin-3-yl) ethylidene-1,1-bisphosphonic acid (minodronate), 1- (4-chlorophenylthio) methylidene-l, 1-bisphosphonic acid (tiludronate), 1- (cycloheptylamino) methylidene-1,1-bisphosphonic acid (cimadronate, incadronate), 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate) and pharmaceutically acceptable salts thereof and mixtures and combinations thereof.

19.(**original**) The composition of claim 1, wherein the bisphosphonate is selected from the group consisting of risedronate, alendronate, pamidronate and their pharmaceutically

acceptable salts and mixtures and combinations thereof.

20.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid is selected from the group consisting of phosphatidyl cholines, phosphatidyl ethanolamines, phosphatidylinositol, phosphatidyl serines sphingomyelin or other ceramides, phospholipid containing oils, and mixtures and combination thereof.

21.(**original**) The composition of claim 1, wherein the zwitterionic phospholipid is selected from the group consisting of phosphatidyl choline (PC), dipalmitoylphosphatidylcholine (DPPC), other disaturated phosphatidyl cholines, lecithin oils and mixture and combinations thereof.

22.(**original**) A pharmaceutical composition, for treating osteoporosis, comprising a pharmaceutically effective amount of a bisphosphonate to reduce bone resorption and a sufficient amount of a zwitterionic phospholipid to reduce GI toxicity and increase the bio-availability of the bisphosphonate.

23.(**original**) The composition of claim 22, the effective amount of the bisphosphonate comprises between about 0.1 mg per dose and about 1000 mg per dose and the sufficient amount of zwitterionic phospholipid is such that a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.1 and about 1:100.

24.(**original**) The composition of claim 22, further comprising a colloidal metal, a metal complex or mixtures or combinations thereof.

25.(**original**) A pharmaceutical composition comprising a carrier, a pharmaceutically effective amount of a bisphosphonate to reduce bone resorption and a sufficient amount of a zwitterionic phospholipid to reduce GI toxicity and increase the bio-availability of the bisphosphonate, where the phospholipid is in its zwitterionic form and the bisphosphonate

is in its zwitterionic form.

26.(**original**) The composition of claim 25, wherein effective amount of the bisphosphonate is between about 0.1 mg per dose and about 1000 mg per dose and the sufficient amount of zwitterionic phospholipid is such that a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.1 and about 1:100.

27.(**original**) The composition of claim 25, further comprising a colloidal metal, a metal complex or mixtures or combinations thereof.

28.(**original**) The composition of claim 25, wherein the medication is to be taken orally.

29.(**original**) The medication of claim 25, wherein the medication is to be taken orally with food.

30.(**original**) An oral medication for treating osteoporosis comprising an solid object comprising an inert carrier, a pharmaceutically effective amount a bisphosphonate to reduce bone resorption and an amount of a zwitterionic phospholipid sufficient to reduce GI toxicity and increase the bio-availability of the bisphosphonate.

31.(**original**) The medication of claim 30, wherein the effective amount of the bisphosphonate is between about 0.1 mg per dose and about 1000 mg per dose and the sufficient amount of zwitterionic phospholipid is such that a ratio of bisphosphonate to zwitterionic phospholipid is between about 1:0.1 and about 1:100.

32.(**original**) The medication of claim 30, further comprising a colloidal metal, a metal complex or a mixture or combination thereof.

33.(**withdrawn**)

34.(**withdrawn**)

35.(**withdrawn**)

36.(**withdrawn**)

37.(**withdrawn**)

38.(**withdrawn**)

39.(**withdrawn**)

40.(**withdrawn**)

41.(**withdrawn**)

42.(**withdrawn**)

43.(**withdrawn**)

44.(**withdrawn**)

45.(**withdrawn**)

46.(**previously added**) A pharmaceutical composition for treating osteoporosis comprising at least one zwitterionic phospholipid and at least one bisphosphonate, where the phospholipid is in its zwitterionic form and the bisphosphonate is in its zwitterionic form.

47.(**previously added**) A pharmaceutical composition, for treating osteoporosis, comprising a pharmaceutically effective amount of a bisphosphonate to reduce bone resorption and a sufficient amount of a zwitterionic phospholipid to reduce GI toxicity and increase the bio-availability of the bisphosphonate, where the phospholipid is in its zwitterionic form and the bisphosphonate is in its zwitterionic form.

48.(**previously added**) An oral medication for treating osteoporosis comprising an solid object comprising an inert carrier, a pharmaceutically effective amount a bisphosphonate to reduce bone resorption and an amount of a zwitterionic phospholipid sufficient to reduce GI toxicity and increase the bio-availability of the bisphosphonate, where the phospholipid is in its zwitterionic form and the bisphosphonate is in its zwitterionic form.